Systems biology

HGPEC: a Cytoscape plugin for prediction of novel disease-gene and disease-disease associations and evidence collection based on a random walk on heterogeneous network

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About
HGPEC Ver 1.0
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Download: http://hgpec.sourceforge.net/
OK

User Manual

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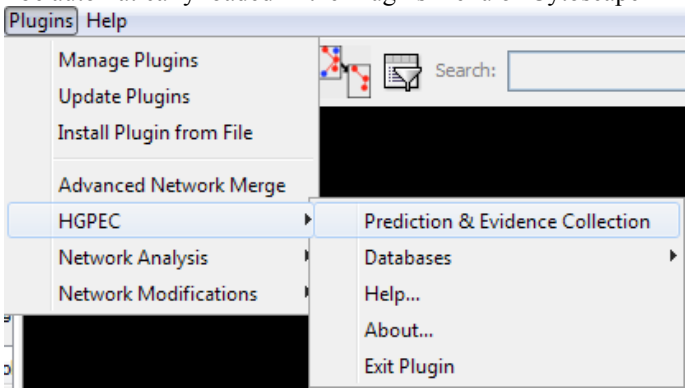
I. Setup

- HGPEC can only run on **Cytoscape 2.x** platform, therefore user should download Cytoscape version 2.x (from 2.7 to 2.8.3) at http://cytoscape.org/download_old_versions.html
- Cytoscape need JRE to run, therefore download JRE version 7.x or later from http://www.oracle.com/technetwork/java/index.html and install it.
- Install Cytoscape to the root folder (e.g., C:\Program Files\Cytoscape_v2.8.3\).
- Download HGPEC.jar file from http://hgpec.sourceforge.net/ and store in **plugins** folder (e.g., C:\Program Files\Cytoscape_v2.8.3\plugins).
- Create folders **Data** in the root folder of Cytoscape (e.g., C:\Program Files\Cytoscape_v2.8.3\).
- Download GO annotation and GeneRIF data at ftp.ncbi.nlm.nih.gov/gene/DATA/gene2go.gz and ftp://ftp.ncbi.nih.gov/gene/GeneRIF/generifs_basic.gz, respectively, then extract and store in the **Data** folder (e.g., C:\Program Files\Cytoscape_v2.8.3\Data).
- Set the maximum heap size to at least 1000MB by opening the file **Cytoscape.vmoptions** (which is located in the Cytoscape root folder) and change corresponding line to -Xmx1000m.

(Demonstration on next pages was done on Windows 7/8 and Cytoscape 2.8.3)

II. Overview of HGPEC

Run Cytoscape, HGPEC will be automatically loaded in the Plugins menu of Cytoscape

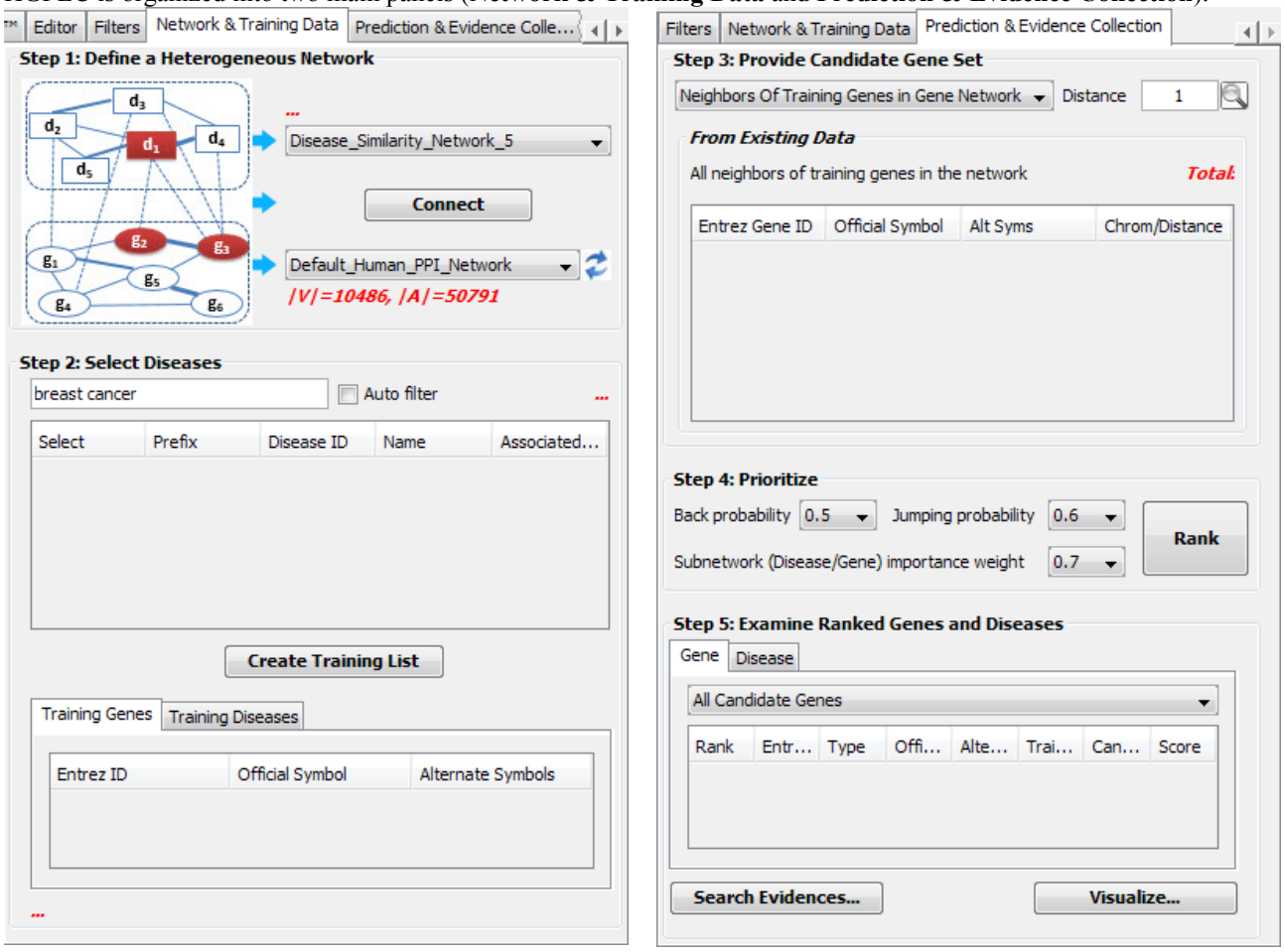


HGPEC has the following menu items:

- **Prediction & Evidence Collection**: This contains main functions of HGPEC
- **Databases**: This shows pre-installed data in HGPEC. It also contains links to GO annotation and GeneRIF data sources.
- **Help…, About…**, and **Exit Plugin**: To show user manual, additional information of HGPEC, and to close HPGEC panels from Cytoscape.

Run HGPEC by clicking menu item **Prediction & Evidence Collection**. HGPEC loads pre-installed data at the beginning.

HGPEC is organized into two main panels (**Network & Training Data** and **Prediction & Evidence Collection**).



The main tasks (Prediction of Genes and Diseases, and Evidence Collection) of HGPEC are completed after five steps:

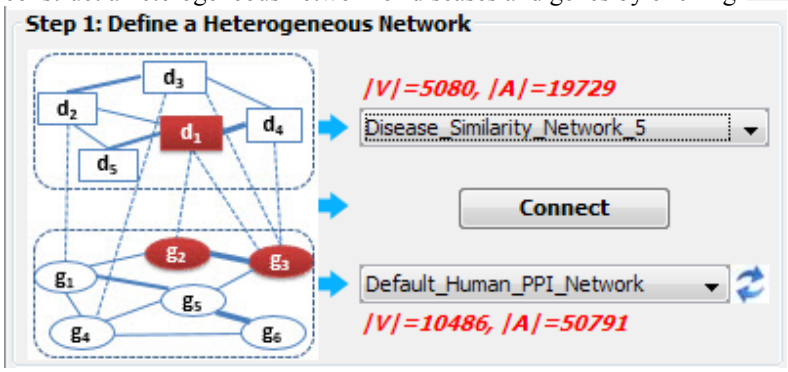
- **Step 1**: Define a Heterogeneous network
- **Step 2**: Select Diseases of interest
- **Step 3**: Provide Candidate Gene Set
- **Step 4**: Prioritize (candidate genes and diseases)
- **Step 5**: Examine Ranked Genes and Diseases

III. Case study: Prediction of novel breast cancer-associated genes and diseases

In the following section, we show the ability of HPEC in identifying novel breast cancer-associated genes and diseases.

III.1. Step 1: Construct a heterogeneous network

To this end, we select a phenotypic disease similarity network containing 5,080 diseases and 19,729 interactions (i.e., **Disease_Similarity_Network_5**) and a human protein interaction network containing 10,486 genes and 50,791 interactions (i.e., **Default_Human_PPI_Network**). Then, we connect them by known disease-gene associations to construct a heterogeneous network of diseases and genes by clicking Connect



To construct a heterogeneous network:

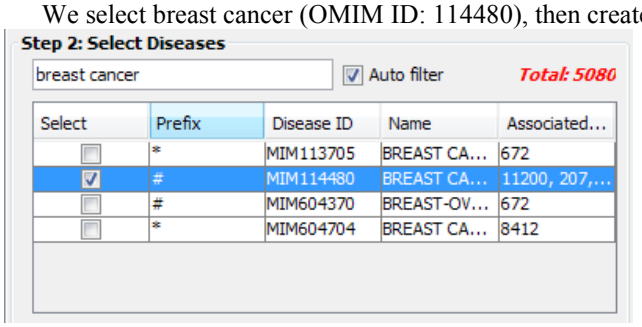
1. *Select a disease similarity network.*
2. *Select a network of genes/proteins (e.g., the preinstalled one or one imported from Cytoscape).*
3. *Click* Connect *to connect these two networks by known disease-gene associations.*

Note that:

- *For disease similarity network: We pre-installed 3 networks corresponding to 5, 10 or 15 nearest neighbors, which were extracted from a phenotypic disease similarity matrix data collected from (van Driel, et al., 2006)*
- *For gene/protein interaction network:*
  - *We pre-installed a human physical protein interaction network collected from ftp://ftp.ncbi.nlm.nih.gov/gene/GeneRIF/interactions.gz.*
  - *However, user can use other protein/gene interaction networks by importing them to Cytoscape (File → Import → Network from table (Text/MS Excel)…). Genes/Proteins in the network must be identified by Gene Entrez ID. After that, click* *to load the imported network to network list.*

III.2. Step 2: Select a disease of interest

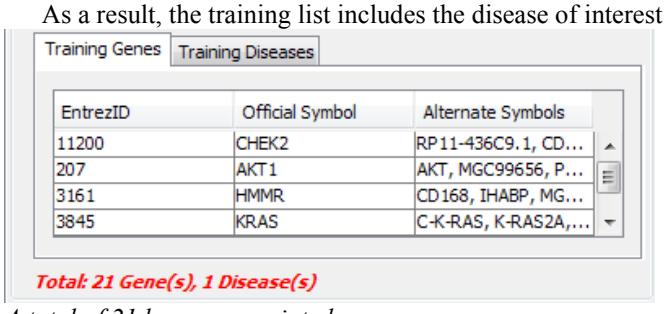
We select breast cancer (OMIM ID: 114480), then create training list by click Create Training List.



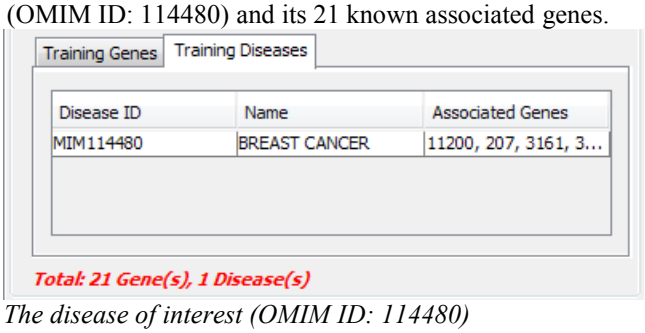
Note that:

- *To quickly select a disease of interest, user should type a keyword then check* **Auto filter**

As a result, the training list includes the disease of interest (OMIM ID: 114480) and its 21 known associated genes.



A total of 21 known associated genes

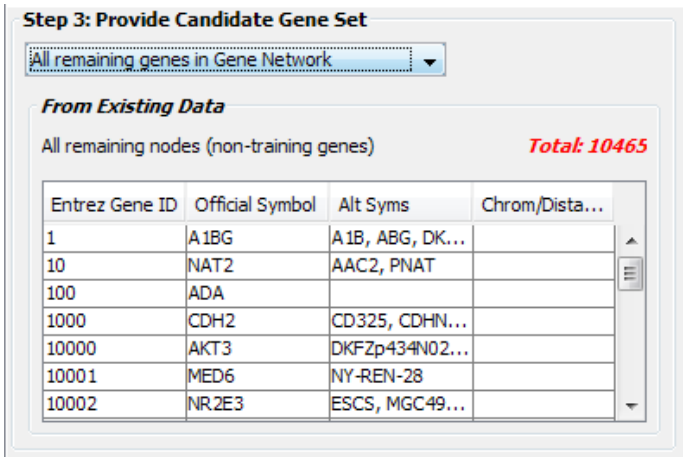


The disease of interest (OMIM ID: 114480)

III.3. Step 3: Select candidate sets

For candidate diseases, all remaining diseases are specified as candidate diseases by default. Therefore, there are 5,079 diseases in this set.

For candidate genes, we select option **All remaining genes in Gene Network**. As a result, a total of 10,465 remaining genes were selected as candidate genes.

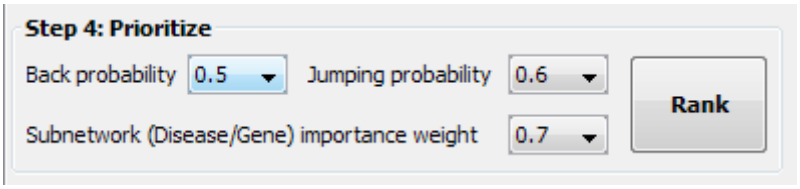


Five ways to construct a candidate gene set:

- **Neighbors of Training Genes in Gene Network**
  - User must define distance of neighbors to training genes
- **Neighbors Of Training Genes in Chromosome** (also known as **Artificial Linkage Interval**)
  - User must define number of neighbors of each training gene in the same chromosome.
- **All remaining genes in Gene Network**
- **Susceptible Chromosome Regions/Bands**
  - User selects candidate genes from susceptible chromosome regions/bands.
- **User-defined**
  - User manually provides a set of candidate genes by Entrez Gene ID or Gene Symbol.

III.4. Step 4: Prioritize candidate genes and diseases in the heterogeneous network

We set three parameters (i.e., back-probability (γ), jumping probability (λ) and subnetwork (Disease/Gene) importance (η)) of RWRH algorithm to 0.5, 0.6 and 0.7, respectively. Please refer to (Li and Patra, 2010) for best parameter setting.

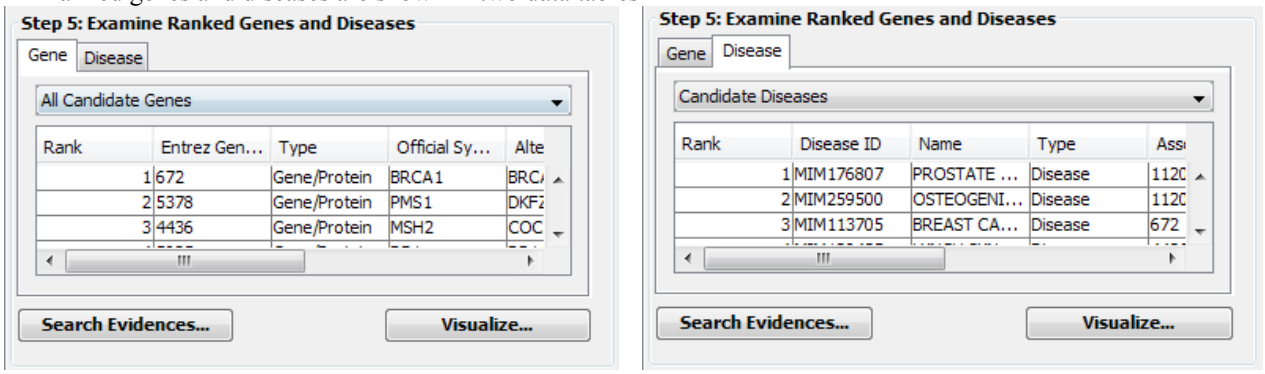


Then click

to rank all candidate genes and diseases in the heterogeneous network

III.5. Step 5: Examine ranked genes and diseases

Ranked genes and diseases are shown in two data tables

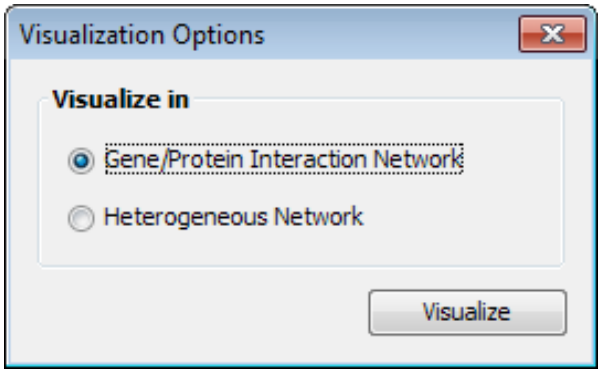


From this interface, user can visualize, annotate and search evidences for novel promising associations between highly ranked candidate genes/ diseases and the disease of interest.

III.5.1. Visualization

Note that, not only candidate genes and diseases are ranked, but all genes and diseases in the heterogeneous network are also ranked. Therefore, user can visualize them in one view to exploit their topologically relationships.

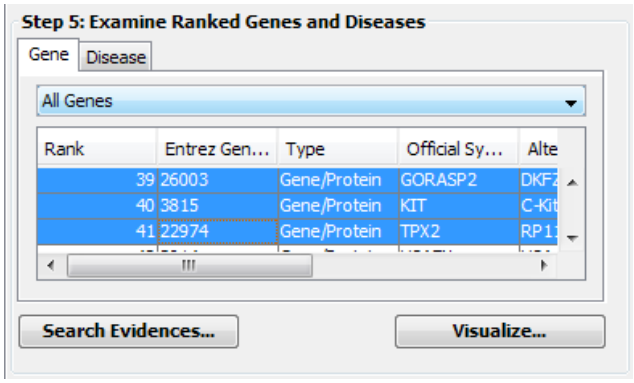
HGPEC provides two options of visualization (**Gene/Protein interaction network** and **Heterogeneous network**)

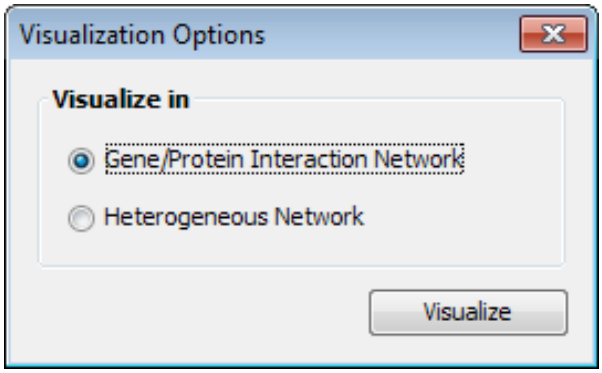


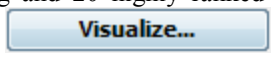
- Option **Gene/Protein interaction network**: Only relationships among selected genes in the gene/protein interaction network are visualized.
- Option **Heterogeneous network**: Relationships between selected genes and diseases in the heterogeneous network are visualized.

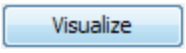
Topological relationships between highly ranked candidate genes and the disease of interest

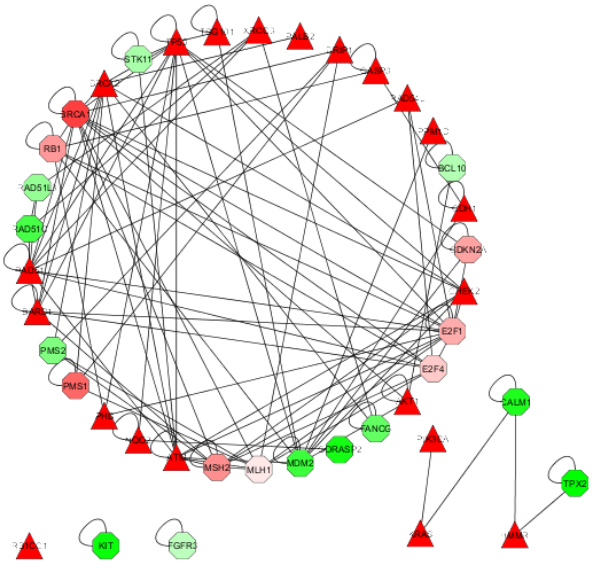
- If we only focus on topological relationships between highly ranked candidate genes and known genes of disease of interest, we should select option **Gene/Protein interaction network**. For example, we selected 20 highly ranked candidate genes and 21 training genes of breast cancer for visualization



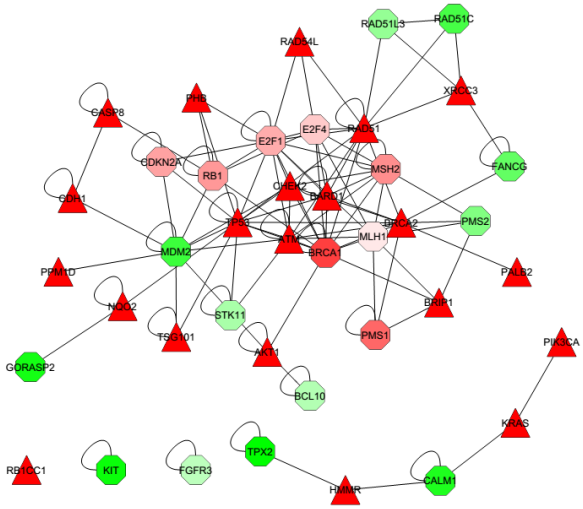


1. Select 21 training and 20 highly ranked candidate genes. Then click 

2. Select option **Gene/Protein interaction network**. Then click 



3. Group Attributes layout (default mode of HGPEC)

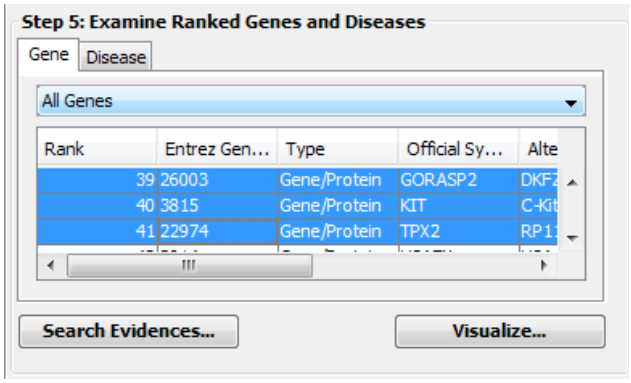


4. Switch to Force-directed Layout (Layout → Cytoscape Layouts → Force-directed Layout)

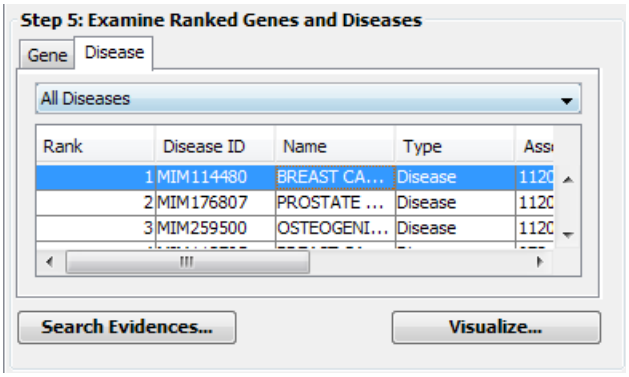
Nodes in triangle shape are training genes, remaining ones are candidates. Nodes with high rankings are in red, relative high are in pink, medium are in white and light green, low are in green.

We found that the sub-network are mostly connected. In other words, highly ranked genes are directly connected to known/training genes

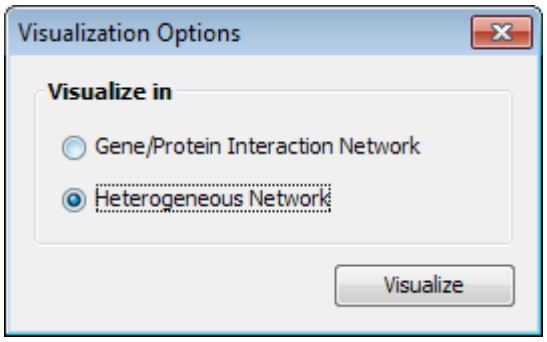
- If we focus on topological relationships between highly ranked candidate genes and disease of interest and its associated genes, we should select option **Heterogeneous network**. For example, we selected top 20 ranked candidate genes, 21 training genes as above and the training disease (i.e., OMIM ID: 114480) for visualization

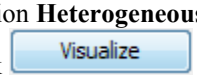


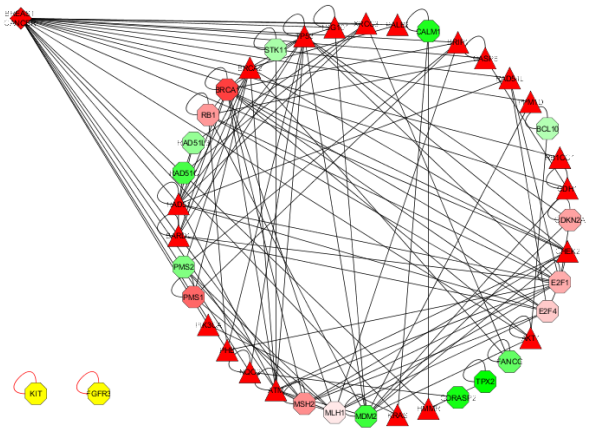
1. Select top 20 ranked candidate genes and 21 training genes.



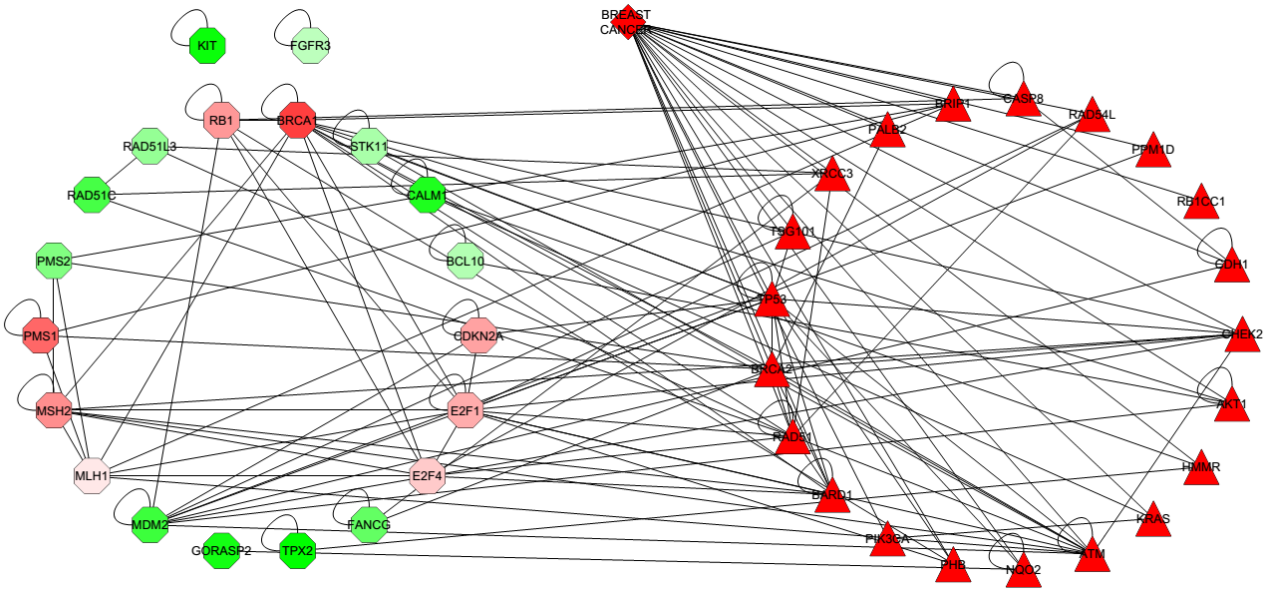
2. Select the training disease (i.e., the disease of interest, OMIM ID: 114480)



3. Select option **Heterogeneous interaction network**. Then click 



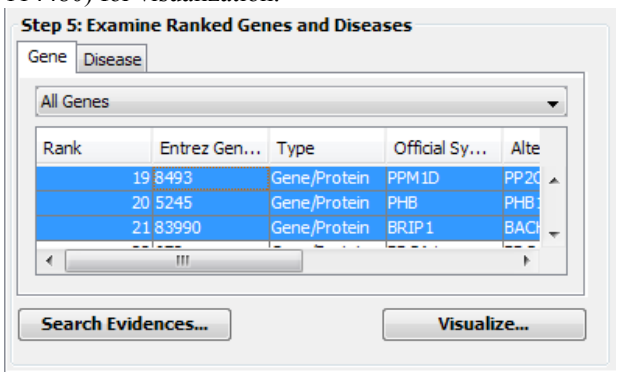
4. Group Attributes Layout with "Type" attribute (default mode of HGPEC)



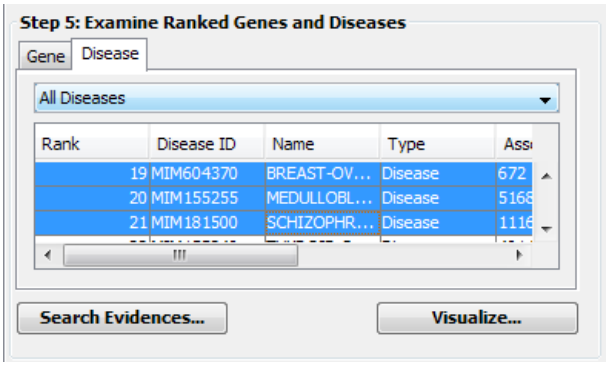
5. Switch to Group attribute layout with "Role" attribute (Layout → Cytoscape Layouts → Group Attributes Layout → Role)
Node in rhombus shape is the disease of interest. Nodes with high rankings are in red, relative high are in pink, medium are in white and light green, low are in green.

Topological relationships between highly ranked candidate diseases and the disease of interest

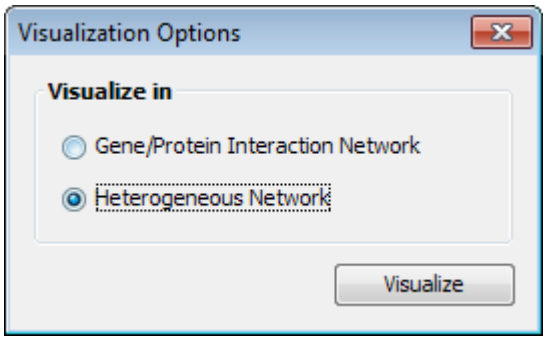
In this case, we selected top 20 ranked candidate diseases, 21 training genes and the disease of interest (i.e., OMIM ID: 114480) for visualization.



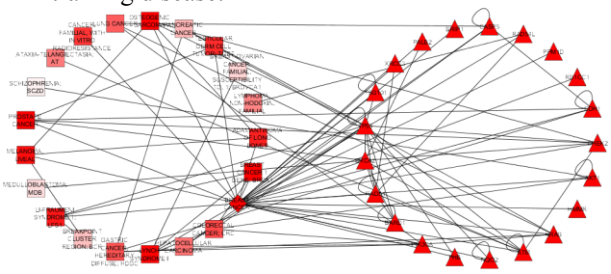
1. Select 21 training genes.



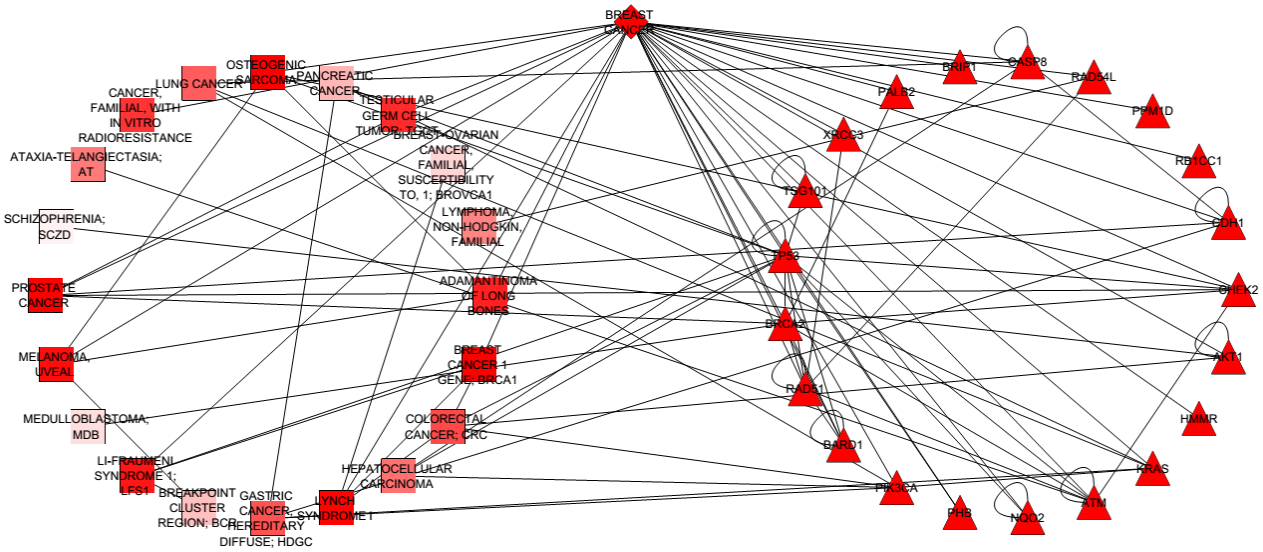
2. Select top 20 ranked candidate diseases and the training disease.



3. Select option **Heterogeneous interaction network**. Then click



4. Group Attributes Layout with "Type" attribute (default mode of HGPEC)



5. Switch to Group attribute layout with "Role" attribute (Layout → Cytoscape Layouts → Group Attributes Layout → Role)

Node in rhombus shape is the disease of interest. Nodes in rectangle shape are candidate diseases. Nodes with high rankings are in red, relative high are in pink, medium are in white and light green, low are in green.

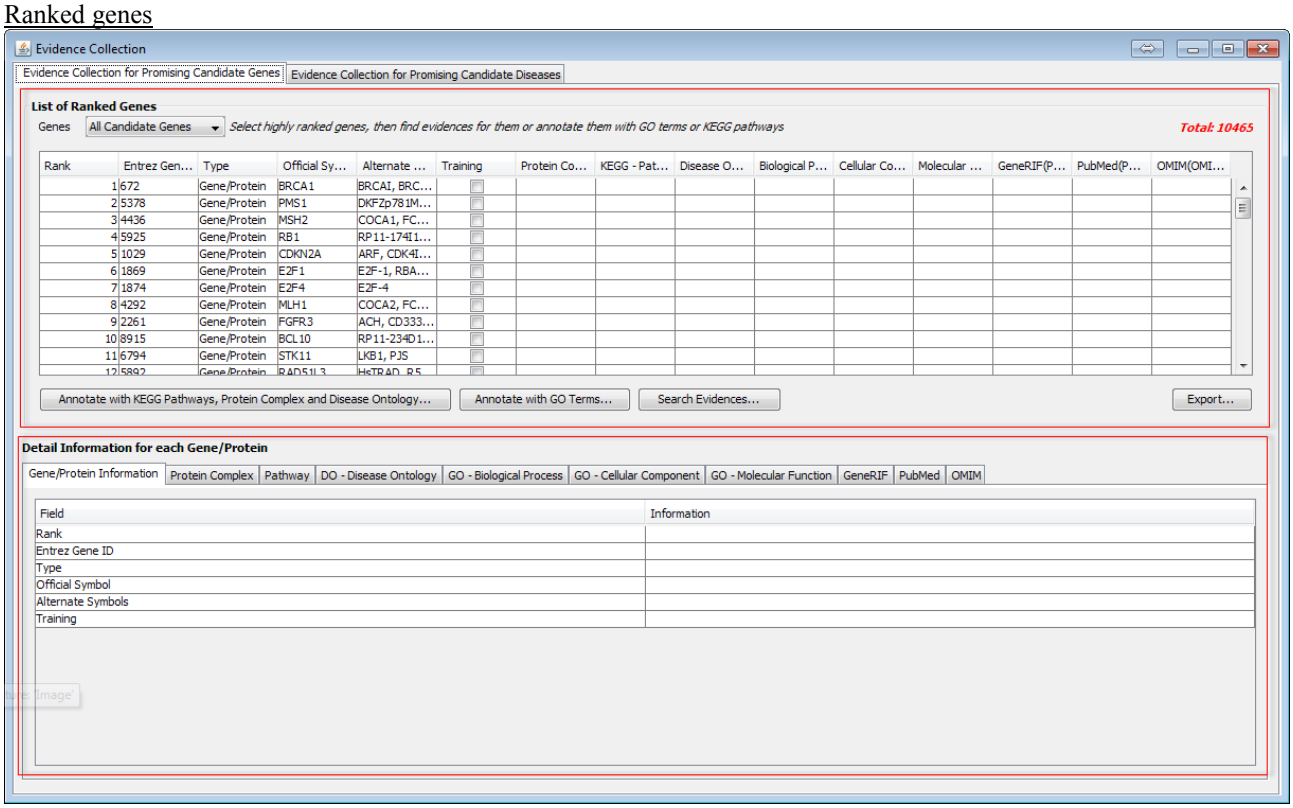
Similarly, we found that the sub-network are connected. In other words, highly ranked candidate diseases are directly connected to either known/training genes or the disease of interest. This means that candidate diseases which have connections to the disease of interest or associated with training genes are highly ranked.

III.5.2. Annotation & Evidence Search

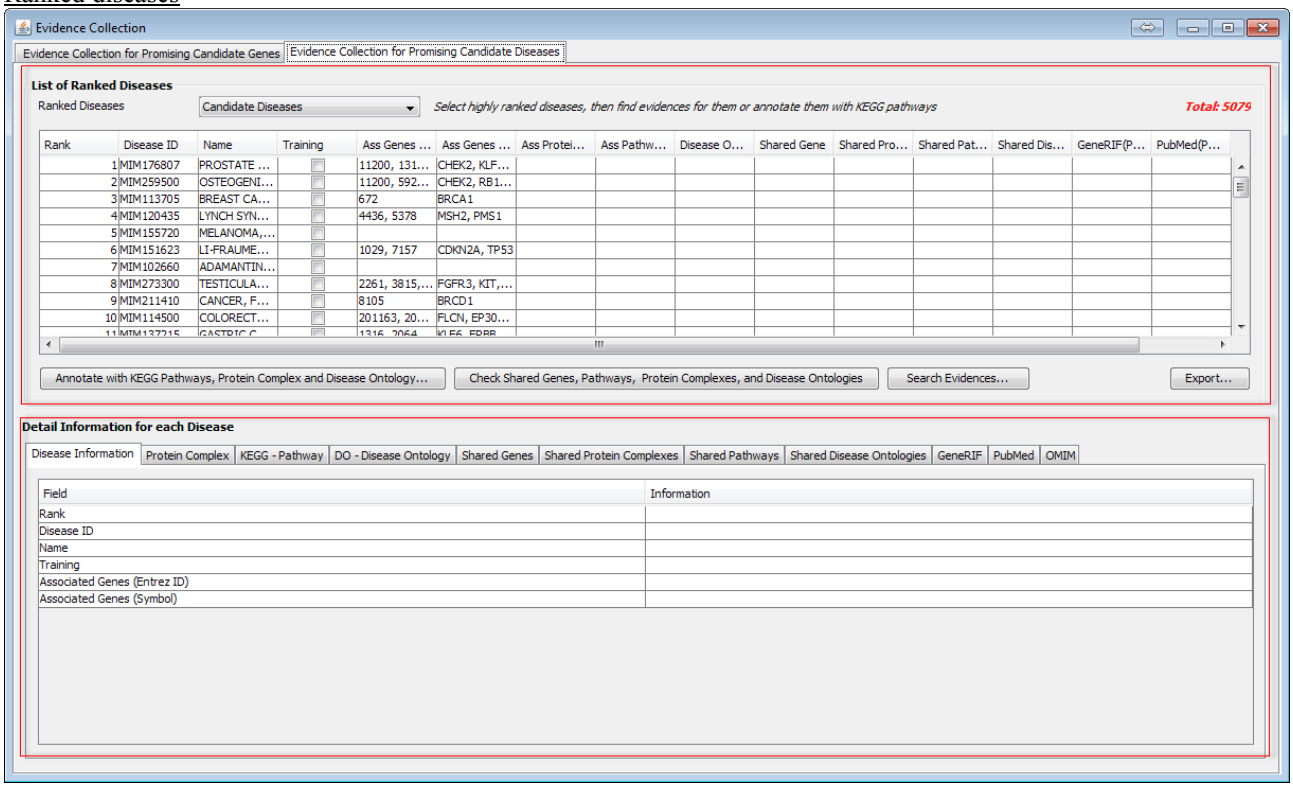
This function is to collect evidences and annotations for associations between highly ranked candidate genes/diseases and the disease of interest.

Ranked genes and diseases are organized in two tabs

Ranked genes



Ranked diseases

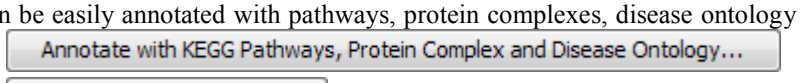


These two tabs are organized as follows:

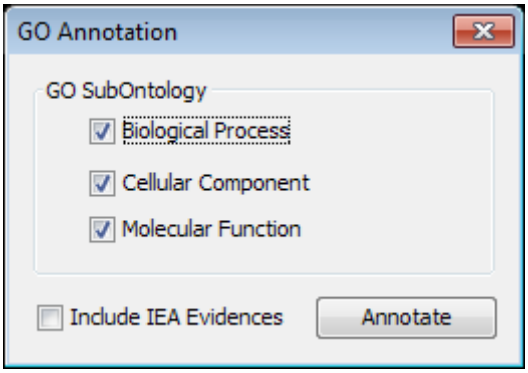
- **Above panel** includes a table data of ranked genes/diseases and functional buttons
- **Below panel** includes tables of annotation and evidence data

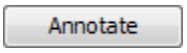
Annotation and evidence collection for associations between highly ranked candidate genes and the disease of interest

We selected top 20 ranked candidate genes for evidence collection.

For annotation, this set can be easily annotated with pathways, protein complexes, disease ontology and gene ontology terms by click 

and

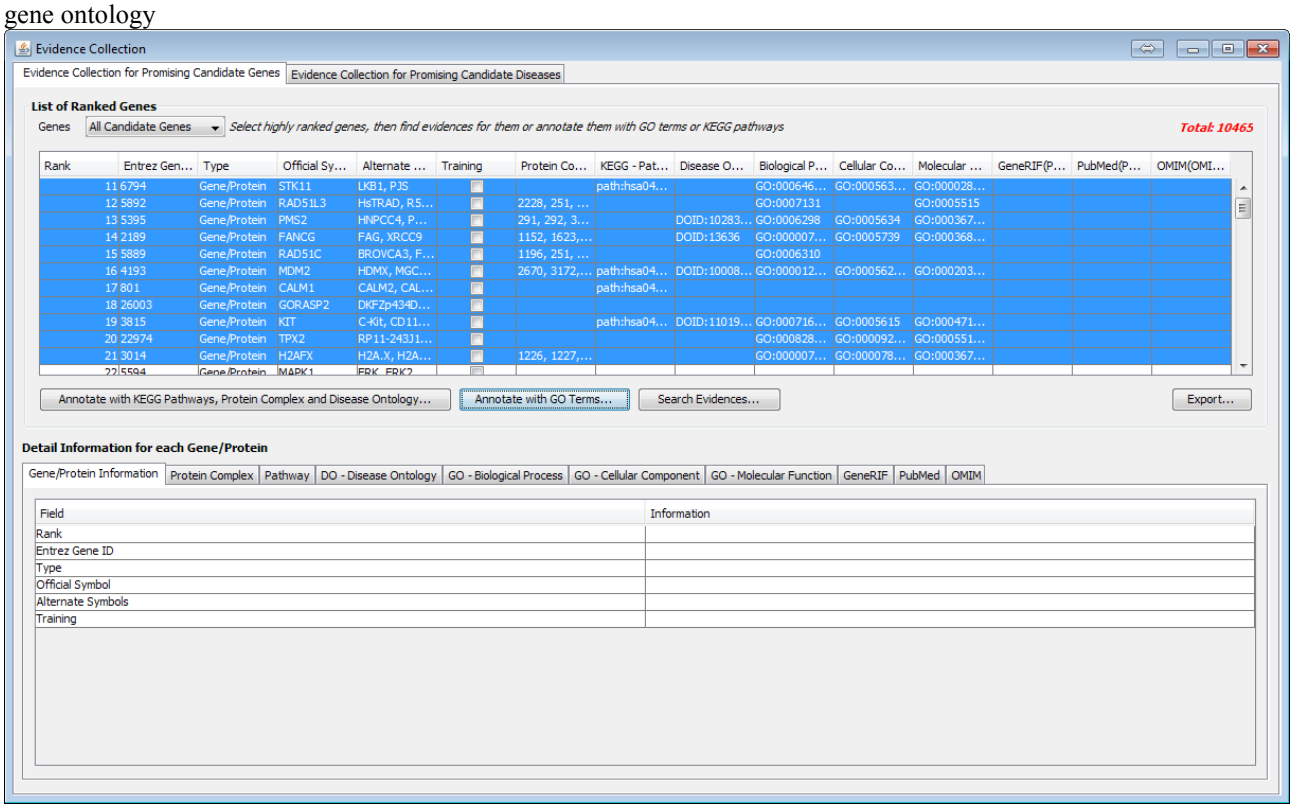


Select GO sub-ontology and whether or not IEA evidence is included. Then click 

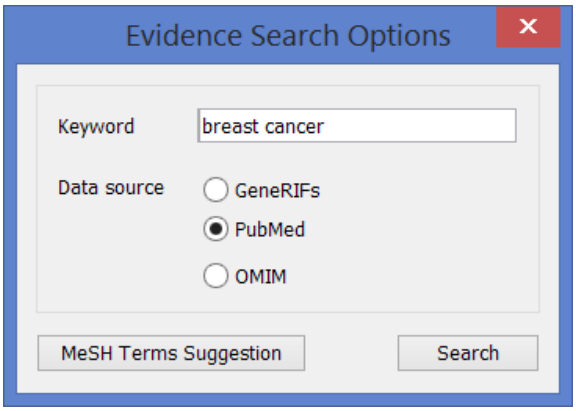
Note that:

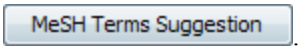
- *GO Annotation data must be downloaded from ftp.ncbi.nlm.nih.gov/gene/DATA/gene2go.gz, then extracted and stored in Data folder in Cytoscape folder (e.g., C:\Program Files\Cytoscape_v2.8.3\Data).*

As a result, the top 20 ranked candidate genes are annotated with pathways, protein complexes, disease ontology and gene ontology


Evidence Collection
Evidence Collection for Promising Candidate Genes
Evidence Collection for Promising Candidate Diseases
List of Ranked Genes
Genes
All Candidate Genes
Select highly ranked genes, then find evidences for them or annotate them with GO terms or KEGG pathways
Total: 10465
Rank
Entrez Gen...
Type
Official Sy...
Alternate ...
Training
Protein Co...
KEGG - Pat...
Disease O...
Biological P...
Cellular Co...
Molecular ...
GeneRIF(P...
PubMed(P...
OMIM(OMI...
11 6794 Gene/Protein STK11 LKB1, PJS path:hsa04... GO:000646... GO:000563... GO:000028...
12 5892 Gene/Protein RAD51L3 HsTRAD, R5... 2228, 251, ... GO:0007131 GO:0005515
13 5395 Gene/Protein PMS2 HNPCC4, P... 291, 292, 3... DOID:10283... GO:0006298 GO:0005634 GO:000367...
14 2189 Gene/Protein FANCG FAG, XRCC9 1152, 1623,... DOID:13636 GO:000007... GO:0005739 GO:000368...
15 5889 Gene/Protein RAD51C BROVCA3, F... 1196, 251, ... GO:0006310
16 4193 Gene/Protein MDM2 HDMX, MGC... 2670, 3172,... path:hsa04... DOID:10008... GO:000012... GO:000562... GO:000203...
17 801 Gene/Protein CALM1 CALM2, CAL... path:hsa04...
18 26003 Gene/Protein GORASP2 DKFZp434D...
19 3815 Gene/Protein KIT C-Kit, CD11... path:hsa04... DOID:11019... GO:000716... GO:0005615 GO:000471...
20 22974 Gene/Protein TPX2 RP11-243J1... GO:000828... GO:000092... GO:000551...
21 3014 Gene/Protein H2AFX H2A.X, H2A... 1226, 1227,... GO:000007... GO:000078... GO:000367...
Annotate with KEGG Pathways, Protein Complex and Disease Ontology...
Annotate with GO Terms...
Search Evidences...
Export...
Detail Information for each Gene/Protein
Gene/Protein Information
Protein Complex
Pathway
DO - Disease Ontology
GO - Biological Process
GO - Cellular Component
GO - Molecular Function
GeneRIF
PubMed
OMIM
Field
Information
Rank
Entrez Gene ID
Type
Official Symbol
Alternate Symbols
Training

For association evidence search, promising associations between these selected candidate genes and the disease of interest can be collected from **GeneRIF** (Mitchell, et al., 2003; Osborne, et al., 2007), **PubMed** (Chang, et al., 2006) and **OMIM** (Amberger, et al., 2009; Hamosh, et al., 2005).



Enter a keyword for disease of interest or select a corresponding MeSH term by clicking 

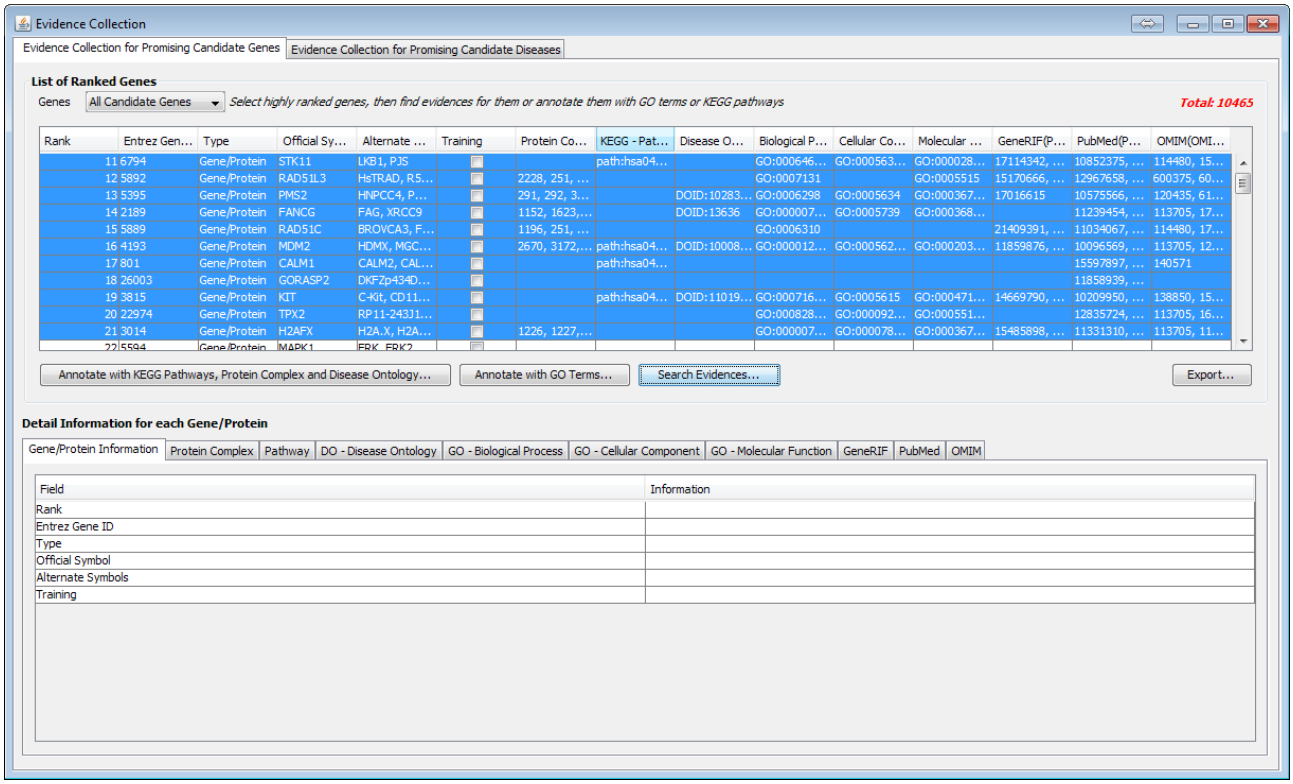
. After that, select a data source among the three ones (i.e., GeneRIF, PubMed and OMIM), then click

. Please wait while HPGEC is updating detail information about found PubMed and OMIM records.

Note that:

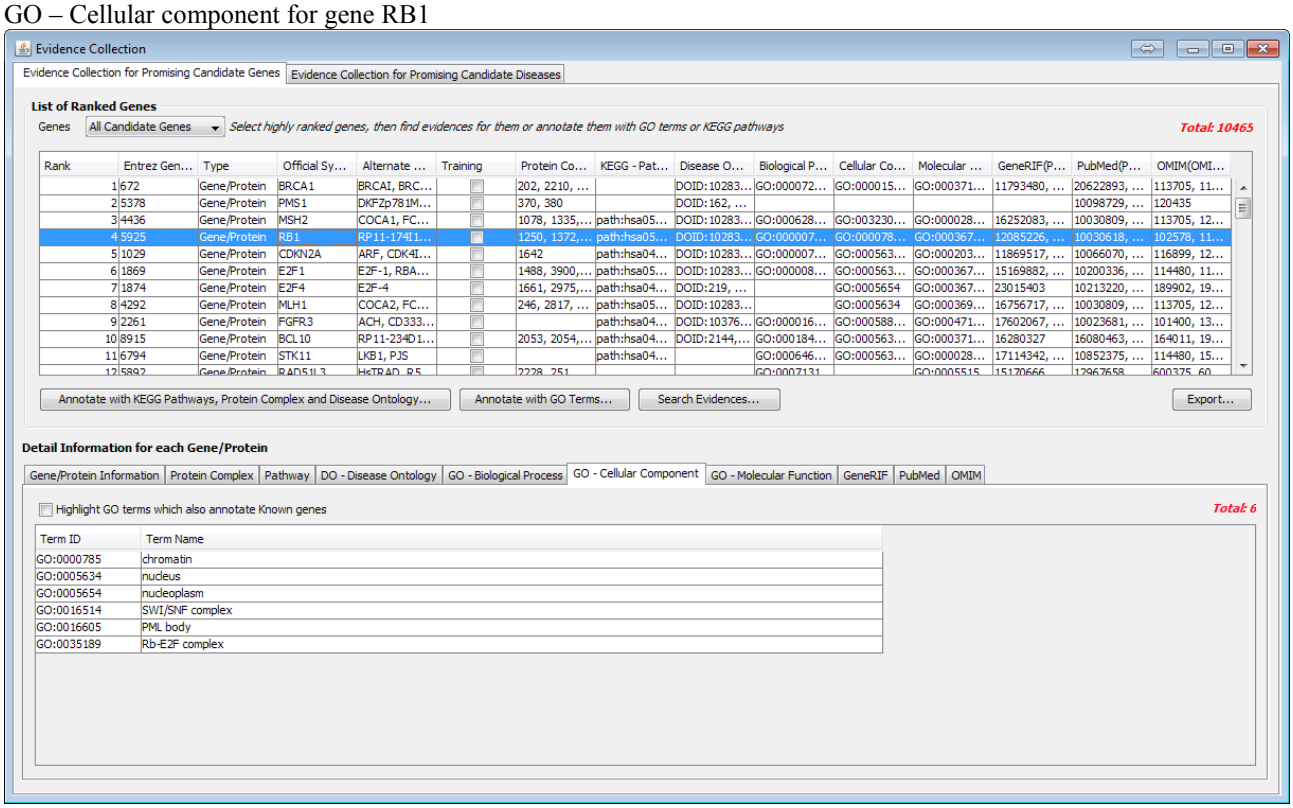
- *For GeneRIF, GeneRIF data must be downloaded from ftp://ftp.ncbi.nih.gov/gene/GeneRIF/generifs_basic.gz, then extracted and stored in Data folder in Cytoscape folder (e.g., C:\Program Files\Cytoscape_v2.8.3\Data).*
- *For PubMed and OMIM, HGPEC automatically search the association between the keyword and the disease of interest from PubMed and OMIM using NCBI web services.*

Here are the result after repeating the above procedure three times for the three data sources.


Evidence Collection
Evidence Collection for Promising Candidate Genes
Evidence Collection for Promising Candidate Diseases
List of Ranked Genes
Genes
All Candidate Genes
Select highly ranked genes, then find evidences for them or annotate them with GO terms or KEGG pathways
Total: 10465
Rank
Entrez Gen...
Type
Official Sy...
Alternate ...
Training
Protein Co...
KEGG - Pat...
Disease O...
Biological P...
Cellular Co...
Molecular ...
GeneRIF(P...
PubMed(P...
OMIM(OMI...
11 6794 Gene/Protein STK11 LKB1, PJS path:hsa04... GO:000646... GO:000563... GO:000028... 17114342, ... 10852375, ... 114480, 15...
12 5892 Gene/Protein RAD51L3 HsTRAD, R5... 2228, 251, ... GO:0007131 GO:0005515 15170666, ... 12967658, ... 600375, 60...
13 5395 Gene/Protein PMS2 HNPCC4, P... 291, 292, 3... DOID:10283... GO:0006298 GO:0005634 GO:000367... 17016615 10575566, ... 120435, 61...
14 2189 Gene/Protein FANCG FAG, XRCC9 1152, 1623,... DOID:13636 GO:000007... GO:0005739 GO:000368... 11239454, ... 113705, 17...
15 5889 Gene/Protein RAD51C BROVCA3, F... 1196, 251, ... GO:0006310 2140939 1, ... 11034067, ... 114480, 17...
16 4193 Gene/Protein MDM2 HDMX, MGC... 2670, 3172,... path:hsa04... DOID:10008... GO:000012... GO:000562... GO:000203... 11859876, ... 10096569, ... 113705, 12...
17 801 Gene/Protein CALM1 CALM2, CAL... path:hsa04... 15597897, ... 140571
18 26003 Gene/Protein GORASP2 DKFZp434D... 11858939, ...
19 3815 Gene/Protein KIT C-Kit, CD11... path:hsa04... DOID:11019... GO:000716... GO:0005615 GO:000471... 14669790, ... 10209950, ... 138850, 15...
20 22974 Gene/Protein TPX2 RP11-243J1... GO:000828... GO:000092... GO:000551... 12835724, ... 113705, 16...
21 3014 Gene/Protein H2AFX H2A.X, H2A... 1226, 1227,... GO:000007... GO:000078... GO:000367... 15485898, ... 11331310, ... 113705, 11...
Annotate with KEGG Pathways, Protein Complex and Disease Ontology...
Annotate with GO Terms...
Search Evidences...
Export...
Detail Information for each Gene/Protein
Gene/Protein Information
Protein Complex
Pathway
DO - Disease Ontology
GO - Biological Process
GO - Cellular Component
GO - Molecular Function
GeneRIF
PubMed
OMIM
Field
Information
Rank
Entrez Gene ID
Type
Official Symbol
Alternate Symbols
Training

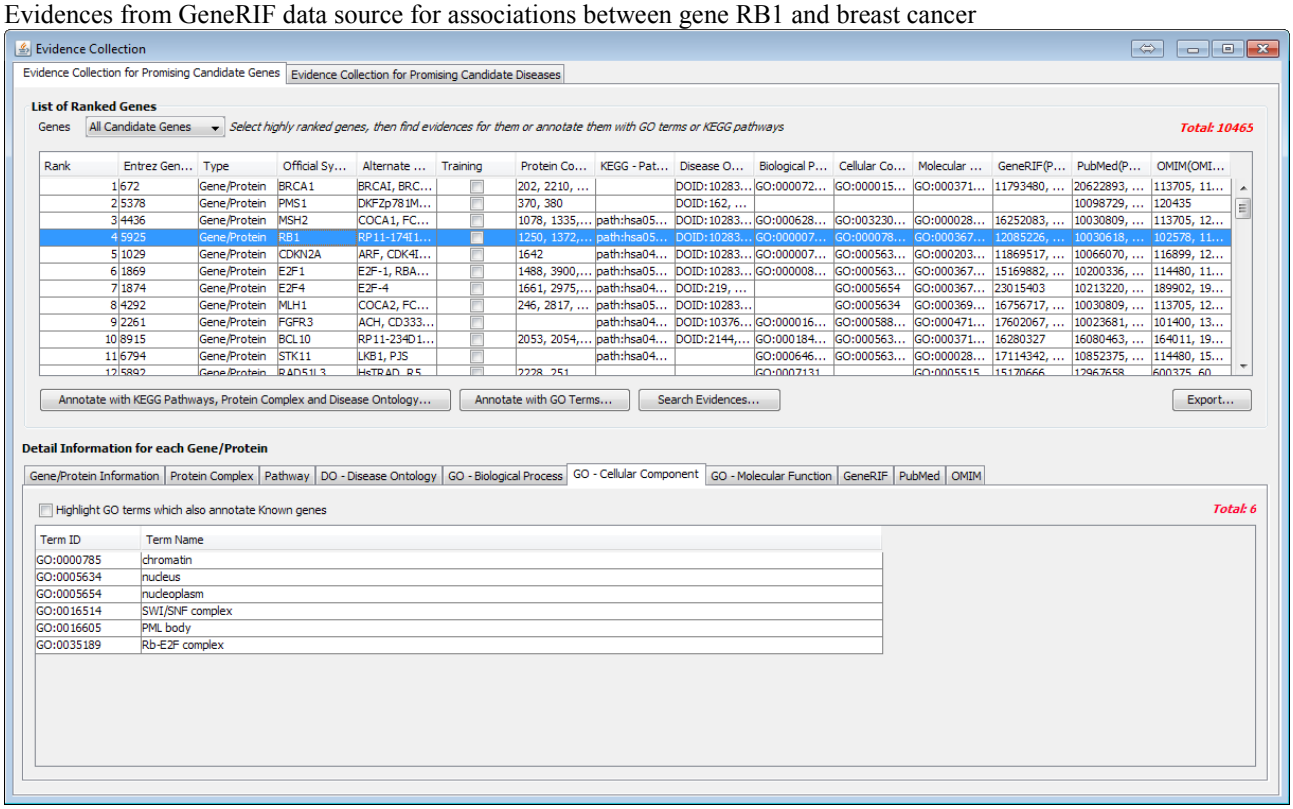
Detail information of annotations (pathway, protein complex, disease ontology and gene ontology) and evidences (PubMed articles, GeneRIF text and OMIM title) can be viewed in lower panels by selecting each gene. For example:

GO – Cellular component for gene RB1



There are six GO cellular component terms annotating to RB1 gene

Evidences from GeneRIF data source for associations between gene RB1 and breast cancer

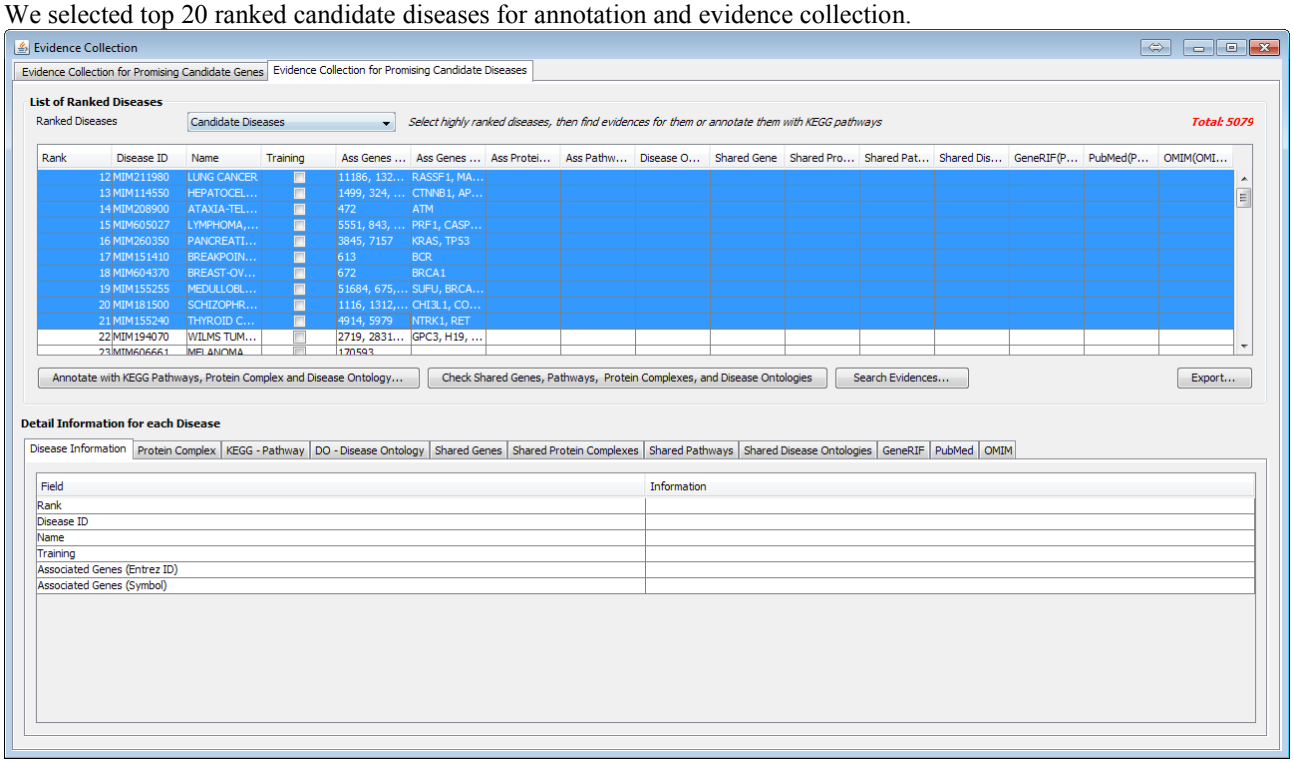


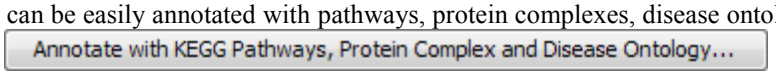
There are 20 PubMed articles whose abstracts contain information about associations between RB1 gene and breast cancer. GeneRIF text are sentences in the abstracts, which contains such the associations.

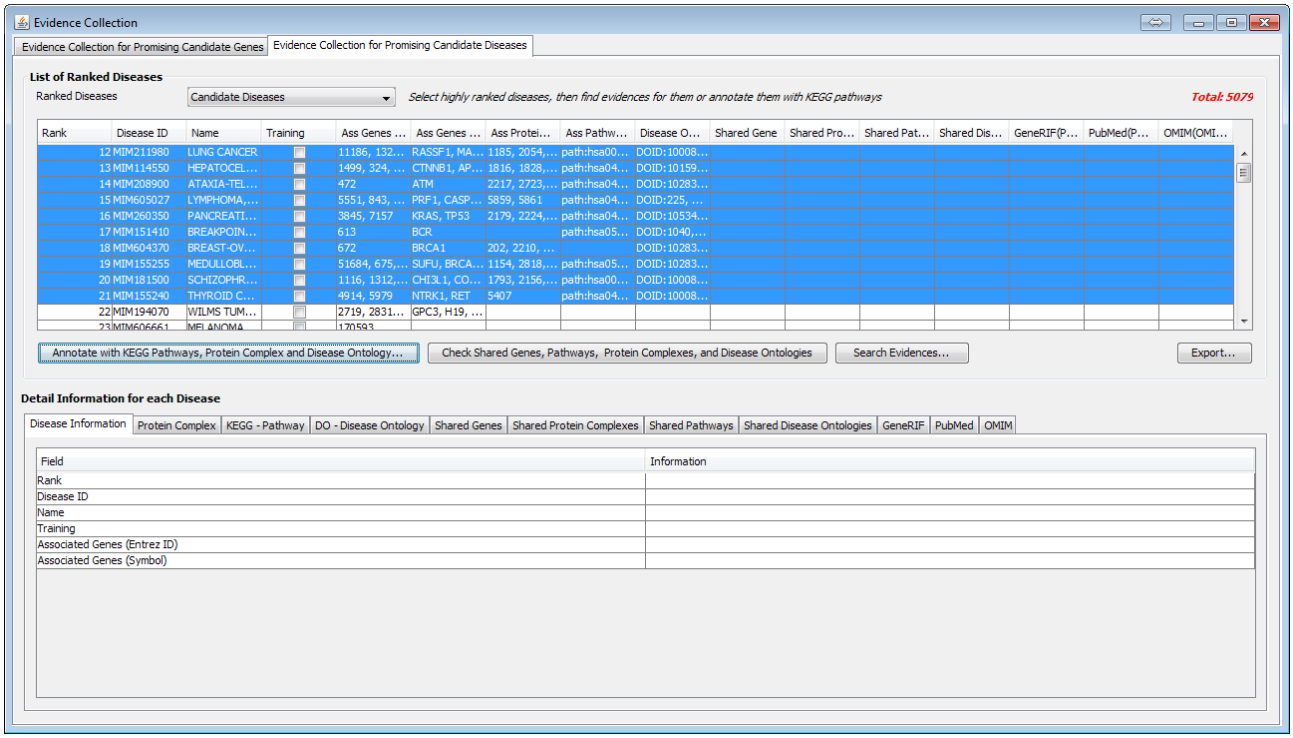
User can also export the selected candidate genes with their annotation and evidence information by clicking Export... . See the exported file in Table S1 in Supplementary Materials

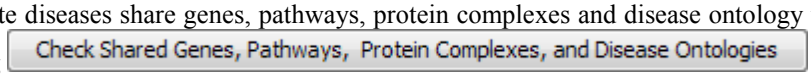
Annotation and evidence collection for relevance between highly ranked candidate diseases and the disease of interest

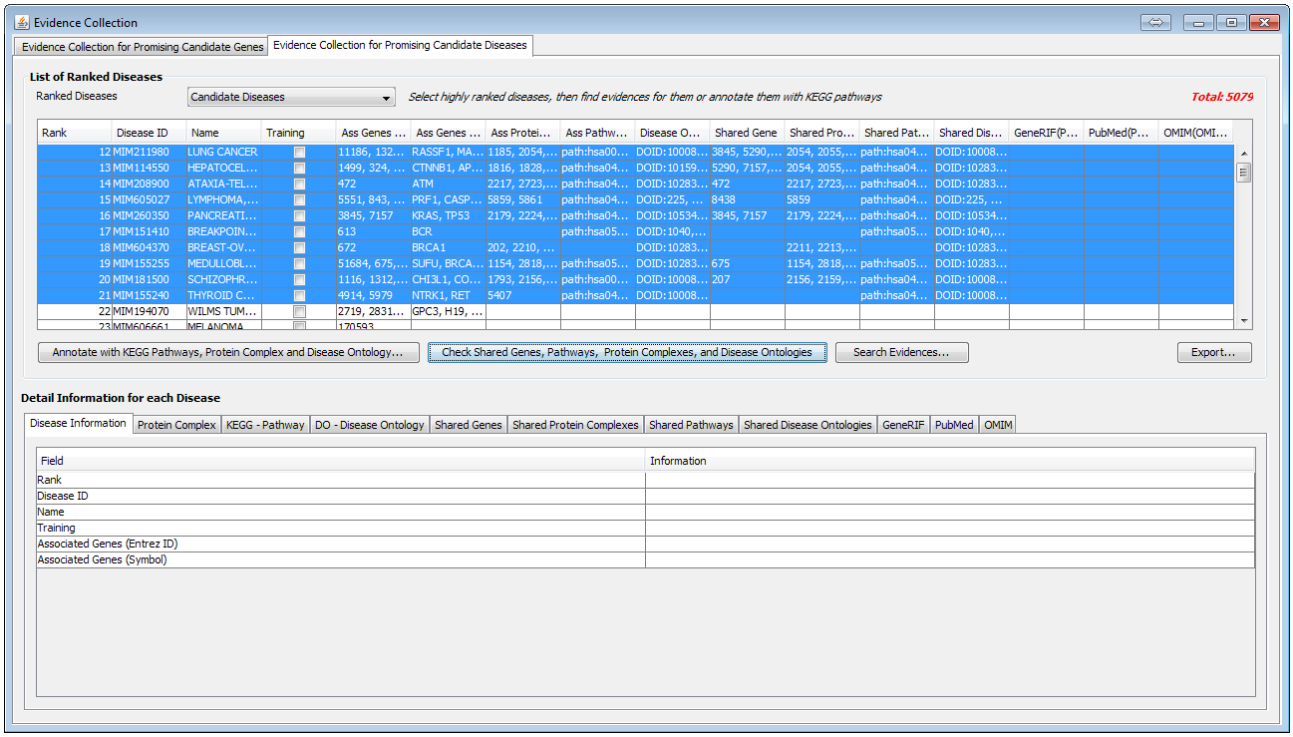
We selected top 20 ranked candidate diseases for annotation and evidence collection.



Similarly, this set can be easily annotated with pathways, protein complexes, disease ontologies and gene ontology (GO) terms by clicking 

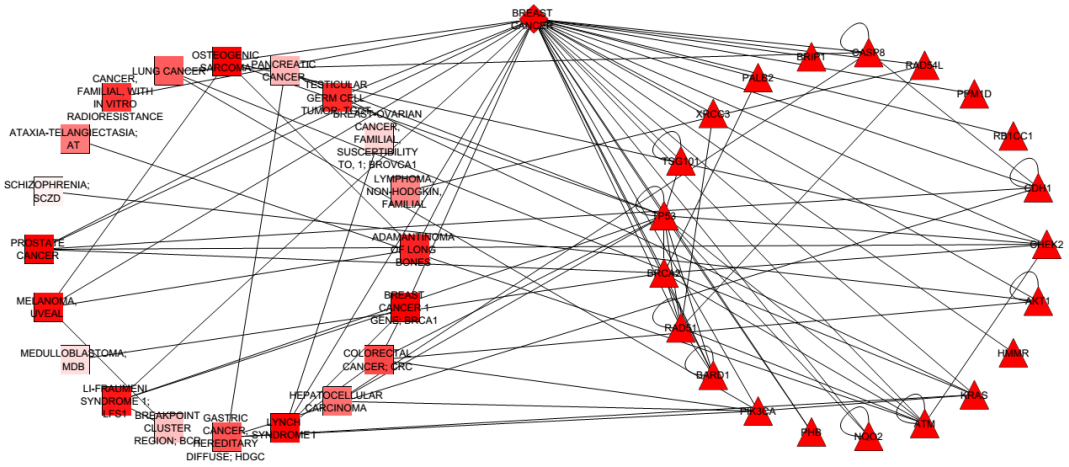

Evidence Collection
Evidence Collection for Promising Candidate Genes
Evidence Collection for Promising Candidate Diseases
List of Ranked Diseases
Ranked Diseases
Candidate Diseases
Select highly ranked diseases, then find evidences for them or annotate them with KEGG pathways
Total: 5079
Rank
Disease ID
Name
Training
Ass Genes ...
Ass Protei...
Ass Pathw...
Disease O...
Shared Gene
Shared Pro...
Shared Pat...
Shared Dis...
GeneRIF(P...
PubMed(P...
OMIM(OMI...
12 MIM211980 LUNG CANCER 11186, 132... RASSF1, MA... 1185, 2054,... path:hsa00... DOID:10008...
13 MIM114550 HEPATOCEL... 1499, 324, ... CTNNB1, AP... 1816, 1828,... path:hsa04... DOID:10159...
14 MIM208900 ATAXIA-TEL... 472 ATM 2217, 2723,... path:hsa04... DOID:10283...
15 MIM605027 LYMPHOMA,... 5551, 843, ... PRF1, CASP... 5859, 5861 path:hsa04... DOID:225, ...
16 MIM260350 PANCREATI... 3845, 7157 KRAS, TP53 2179, 2224,... path:hsa04... DOID:10534...
17 MIM151410 BREAKPOIN... 613 BCR path:hsa05... DOID:1040,...
18 MIM604370 BREAST-OV... 672 BRCA1 202, 2210, ... DOID:10283...
19 MIM155255 MEDULLOBL... 51684, 675,... SUFU, BRCA... 1154, 2818,... path:hsa05... DOID:10283...
20 MIM181500 SCHIZOPHR... 1116, 1312,... CHI3L1, CO... 1793, 2156,... path:hsa00... DOID:10008...
21 MIM155240 THYROID C... 4914, 5979 NTRK1, RET 5407 path:hsa04... DOID:10008...
22 MIM194070 WILMS TUM... 2719, 2831... GPC3, H19, ...
Annotate with KEGG Pathways, Protein Complex and Disease Ontology...
Check Shared Genes, Pathways, Protein Complexes, and Disease Ontologies
Search Evidences...
Export...
Detail Information for each Disease
Disease Information
Protein Complex
KEGG - Pathway
DO - Disease Ontology
Shared Genes
Shared Protein Complexes
Shared Pathways
Shared Disease Ontologies
GeneRIF
PubMed
OMIM
Field
Information
Rank
Disease ID
Name
Training
Associated Genes (Entrez ID)
Associated Genes (Symbol)

Note that, a number of studies have defined associations between diseases based on their shared associated genes (Goh, et al., 2007), shared protein complexes (Wang, et al., 2012), shared pathway (Li and Agarwal, 2009) and shared disease ontology (Li, et al., 2011). Therefore, in addition to annotate each disease in the top ranked candidate diseases with pathways, protein complexes and disease ontology terms, we provided a function to check whether or not these selected candidate diseases share genes, pathways, protein complexes and disease ontology terms with the disease of interest by clicking 

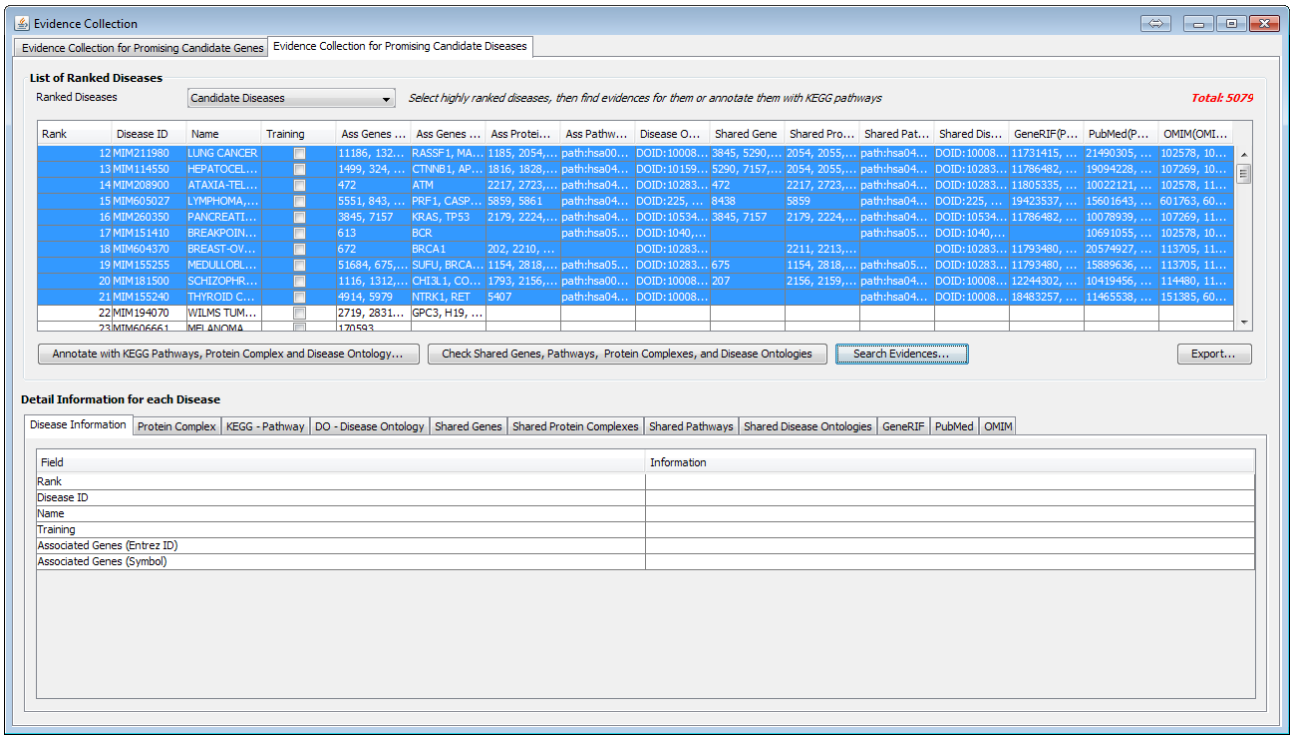


Further analyzing the above result, we found that

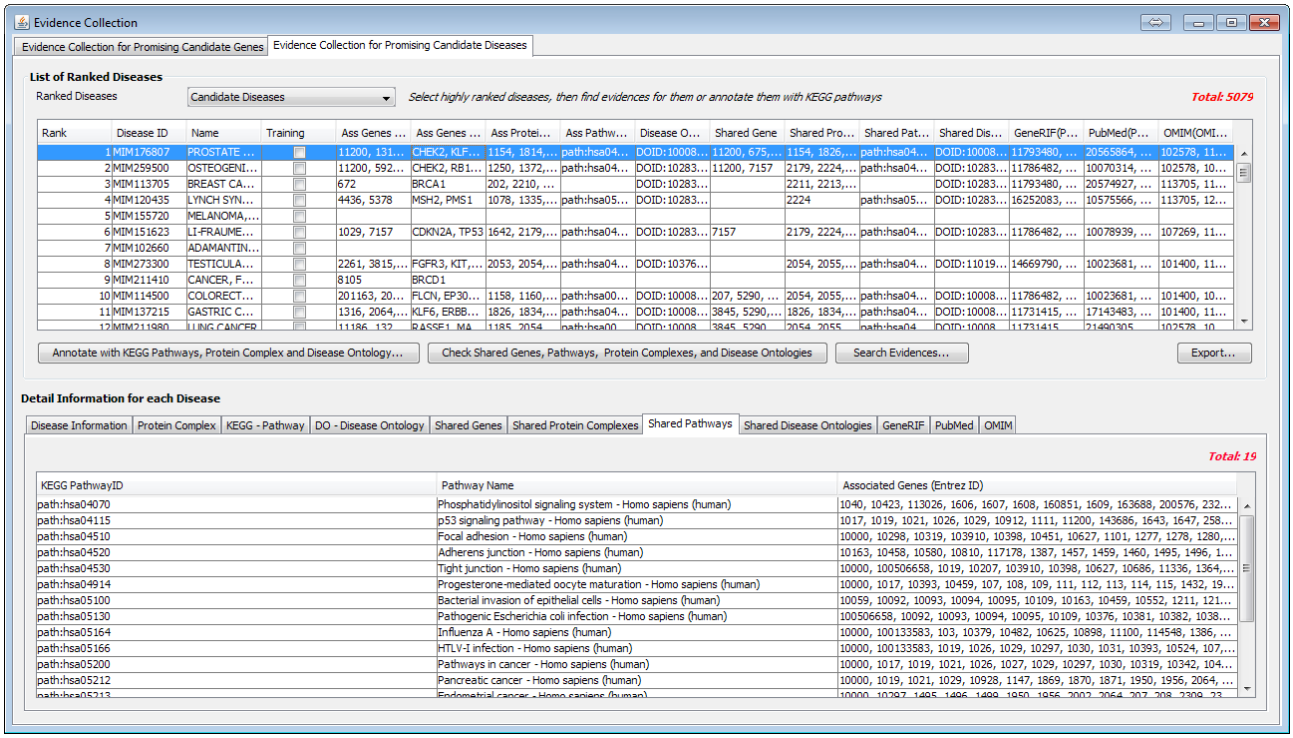
- Twelve of 20 selected candidate diseases (Ranks: 1, 2, 6, 10, 11, 12, 13, 14, 15, 16, 19 and 20) have at least one gene, pathway, protein complex and disease ontology term shared with the disease of interest.
- Five of 20 selected candidate diseases (Ranks: 3, 4, 8, 17 and 18) have at least one pathway, protein complex and disease ontology term shared with the disease of interest. However, they do not have any shared genes with the diseases of interest. This means that if we only based on the shared genes to associate these diseases with the disease of interest, we could not find any association. However, other biomedical data such as pathway, protein complex and disease ontology can provide evidences for their associations.
- The three remaining of 20 selected candidate diseases (Ranks: 5, 7 and 9) do not have any shared gene, shared pathway, shared protein complex and shared disease ontology term with the disease of interest. However, they still have high rankings, which indicates that they highly are associated with the disease of interest. Further investigating their topological relationships with the disease of interest, we found an interesting result that like others in the top 20 selected candidate diseases, these diseases directly connected to the disease of interest (breast cancer (OMIM ID: 114480)) in the phenotypic disease similarity network.



Similarly, information about associations between selected candidate diseases and the disease of interest can be collected from GeneRIF, PubMed and OMIM based on the associations between their known associated genes and the disease of interest.



In a similar way, detail information of annotations (pathways, protein complex and disease ontology) and sharing (genes, pathways, protein complexes and disease ontology terms) can be viewed in lower panels by selecting each disease. For example, here is the result for Prostate cancer (OMIM ID: 176807)



There are 19 common pathways between Prostate cancer (OMIM ID: 176807) and Breast cancer (OMIM ID: 114480)

Similarly, user can also export the selected candidate diseases with their annotation and evidence information by clicking

. See the exported file in Table S2 in Supplementary Materials.

IV. Reference

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